SUMMARY

The present in vivo study was focused on better understanding of the pathophysiological mechanisms contributing to high blood pressure maintenance in spontaneously hypertensive rats (SHR). Genetic hypertension is characterised by abnormally elevated activity of sympathetic nervous system (SNS) and increased sensitivity to catecholamine-induced vasoconstriction comprising both enhanced calcium influx to vascular smooth muscle cells via L-type of voltage-dependent calcium channels (L-VDCC) and altered vascular sensitivity to intracellular calcium mediated by RhoA/Rho-kinase pathway. Thus, our aims were to study the regulation of L-VDCC channels, to determine the role of “calcium sensitization” in hypertension and finally to evaluate which of these pathways is important in the maintenance of high blood pressure.

Using conscious SHR rats and their normotensive controls, WKY, we have confirmed that high sympathetic tone is responsible for increased calcium influx via L-VDCC in hypertension. The experiments based on the pertussis toxin-induced inactivation of inhibitory G proteins (G_i) have revealed that the control of L-VDCC by SNS is mediated by G_i protein-coupled pathway, the elimination of which leads to the attenuation of sympathetic vasoconstriction and to the decrease of blood pressure response to the nifedipine-induced blockade of L-VDCC in hypertensive rats. Moreover, both the inactivation of G_i proteins and/or the blockade of L-VDCC caused a considerable rightward shift of norepinephrine dose-response curves, the effects being non-additive. In addition, G_i protein inactivation caused the augmentation of blood pressure responses to the blockade of BK_{Ca}-dependent vasodilation suggesting that the activity of these channels is increased under these conditions.

Furthermore, we have confirmed our hypothesis that cAMP-induced closure of L-VDCC is mediated by membrane potential changes elicited by the activation of K^+ channels (BK_{Ca} and/or K_V). The inhibition of any of these K^+ channels led to the diminution of cAMP overproduction-induced vasodilator effects in hypertensive rats, while in normotensive rats the absence of one class of K^+ channels can be compensated by the remaining K^+ channel family pointing out the altered function of these K^+ channels in hypertension.

Since smooth muscle contractility is determined by both calcium influx through L-VDCC and RhoA/Rho-kinase-mediated calcium sensitization, we have examined the role of RhoA/Rho-kinase pathway in genetic hypertension. Using Rho kinase inhibitor, fasudil, we have confirmed our hypothesis that maintenance of high blood pressure in SHR rats is more dependent on calcium influx through L-VDCC than on calcium sensitization.

In summary, augmented calcium influx into the vascular smooth muscle via L-VDCC is one of the most important factors responsible for the maintenance of high blood pressure. The increased calcium influx through these calcium channels is a result of elevated sympathetic activity mediated by G_i protein-cAMP-coupled pathway. While the inhibition of cAMP pathway by G_i proteins activation opens L-VDCC, the stimulation of this pathway leads to the inhibition of calcium influx via L-VDCC. The latter is mediated by the activation of BK_{Ca} and K_V channels, the activity of which seems to be different in normotensive and hypertensive rats.